At the Meeting . . .

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For the past decade, investigators have been on the trail of mesenchymal cells in the epidermis, asking whether these cells have an immunological function and, if so, what it is. Now, Georg Stingl reported at the Annual Meeting of The Society for Investigative Dermatology, Inc., at least some of the answers are in. In his Montagna lecture, on May 2, 1986, Stingl noted that not only are the immunological functions of these cells becoming increasingly clear, but their roles in pathologic processes are becoming apparent. In particular, Stingl provided new evidence that Langerhans cells in the epidermis may well be a reservoir for the autoimmune deficiency syndrome (AIDS) virus.

The story begins in 1976 when Inga Silberberg and Rudolf Baer at New York University found the first potential link between immune responsiveness and Langerhans cells. Using electron microscopy, they noticed that Langerhans cells are next to lymphocytes in the skin of patients with contact hypersensitivity and that these Langerhans cells are damaged. This suggested that Langerhans cells might somehow be involved in contact hypersensitivity.

Then, in 1977, Stingl, who was then working with Stephen Katz and his colleagues at the National Institutes of Health, reported that Langerhans cells in human skin express certain antigens on their surfaces and these antigens are typical of immune system cells. In particular, the NIH researchers found that Langerhans cells resemble monocytes or macrophages more than T and B cells. But, says Stingl, "Langerhans cells are very poor phagocytes."

About a year later, Stingl, Katz, and their associates got a partial answer. Langerhans cells, they found, may be capable of stimulating T cells. When they added antigen-bearing Langerhans cells to T cells in vitro, the T cells proliferated. But their Langerhans cells preparations were not pure—they contained keratinocytes, among other cells. At the time, says Stingl, "Keratinocytes were considered innocent bystanders." But it turns out that " . . . keratinocytes turn out a plethora of immune regulatory substances. One of the greatest hazards in science is oversimplification," Stingl remarks.

Another difficulty with concluding from these initial experiments that Langerhans cells are capable of stimulating T cells is that the researchers did not know whether Langerhans cells could stimulate primary resting T cells. Their work showed only that Langerhans cells can stimulate sensitized T cells. Only if the Langerhans cells were indeed capable of initiating a primary immune response could they hold them responsible for inducing the reactions in which they suspected them of playing a critical role—contact hypersensitivity and skin allograft reactions. But it was not until several researchers performed further careful in vitro experiments that it became clear that Langerhans cells can, in fact, stimulate primary resting T cells. Investigators Paul Bergstresser and Wayne Streilein at the Health Science Center, Dallas, Texas, were the first to demonstrate that these in vitro data were of actual in vivo significance. They provided evidence that Langerhans cells are the principal sensitizing cells in the induction of contact hypersensitivity.

But there was still the question of whether it was Langerhans cells or other cells present along with them that were producing these effects. "We had to purify the Langerhans cells to see if they alone were responsible for the T cell response," Stingl says. "It was a Herculean task. Researchers cursed the cells in English, French, German, and Japanese." "Now," says Stingl, "we must confess that we have come very close but that we have not reproducibly achieved this goal. In general, however, we find that the better the purification, the better the T cell sensitization."

Now it is established that Langerhans cells take up antigens, process them, and present them to T cells. Unlike B cells, T cells can only recognize antigens when they are presented by another cell bearing "self" antigens.

Next came the questions of where Langerhans cells come from, where they are going, and to which cell lineage they belong. Langerhans cells as well as macrophages and dendritic cells are derived from and are continually replaced by precursors originating in the bone marrow. "We got the impression that Langerhans cells are somewhere between mononuclear macrophages and dendritic cells," Stingl remarks. "The cell surface antigen distribution could either indicate that Langerhans cells are a transitional phase or a final end product of a unique differentiation pathway of bone marrow-derived cells."

One hint of what might be going on comes from observing Langerhans cells in culture. "Langerhans cells not only survive in culture but undergo profound phenotypic changes," says Stingl. They lose Fc-IgG receptors, ATPase activity, and Birbeck granules, but increase their Ia antigens. In short, they become more and more like dendritic cells. Moreover, there are indications that the same changes might occur with Langerhans cells in vivo. There are veiled cells in the afferent lymphatics and interdigitated cells in the paracortical T-dependent areas of the lymph nodes that are indistinguishable from dendritic cells.

Veiled cells increase in number when Langerhans cells in the skin are exposed to antigens. Hence, one model is that Langerhans cells become veiled cells which become interdigitating cells which then become dendritic cells. But this model has a weakness, Stingl points out. It is known that dendritic cells can be grown directly from bone marrow cells. So, despite the attractiveness of this model, "We cannot exclude the possibility that Langerhans cells are the final product of the monocyte differentiation pathway and that there is a separate pathway for veiled cells and dendritic cells," Stingl says.

Future goals of research on Langerhans cells are to determine the differentiation pathway, the traffic, and the ultimate fate of these cells. Although it may well be that the major function of Langerhans cells is to activate specialized effects of helper T cells, Stingl warns that, "we don't want the concept of Langerhans cells to be too narrow. I strongly believe that these cells have a lot to do at home in the epidermis. The old concepts that Langerhans cells have a scavenger function and that they may influence growth and differentiation of other epidermal cells should be carefully investigated. Finally, let's not forget the quest for the holy grail of Langerhans cell research—Langerhans cell tumorogenesis."

In the meantime, Stingl and his colleagues Erwin Tschachler, Veronika Groh, Klaus Konrad, and Klaus Wolff of the University of Vienna, along with Mica Popovic and Dean Mann of the National Cancer Institute and Bijan Safai from Memorial Sloan Kettering Cancer Center recently obtained evidence linking Langerhans cells to AIDS. They noted that Langerhans cells express

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T4 antigens, which are binding sites for the AIDS virus. So, they asked, might Langerhans cells be a preferential target for the AIDS virus? They obtained skin biopsies from 40 individuals with AIDS or AIDS-Related-Complex and similar biopsies from 84 seronegative persons who served as controls. In approximately 17% of all biopsies from the AIDS or ARC patients, the Langerhans cells were the only epidermal cells to react with monoclonal antibodies against HTLV-III. Moreover, there were viral particles indistinguishable from HTLV-III associated with the Langerhans cells in one of these biopsies. Only one of the controls had Langerhans cells that reacted with the HTLV-III antibody and this was a patient with classical Kaposi's sarcoma. Since the skin is the largest organ of the body and since the biopsies were only very small samples, it remains possible that more than 17% of the Langerhans cells from these AIDS and ARC patients contain the virus. "We believe these data strongly suggest that Langerhans cells are a target and a potential reservoir for the AIDS virus," Stingl says.

AIDS virus is only rarely found in circulating T cells of patients, probably because it kills these cells so quickly that either they are destroyed or are present and uninfected. So the finding of the virus in Langerhans cells is potentially very important. It may have adverse consequences for the immunological functions of this cell system, and may thus contribute to both the acquisition of immunodeficiency and the infectious and neoplastic consequences of AIDS.

The past decade of intensive study of Langerhans cells has been enormously fruitful. But, as the AIDS work indicates, it may well be that the most interesting findings are yet to come.